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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,734	07/14/2003	Gregory Gregoriadis	G0365.0365/P0365	3606

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,734	GREGORIADIS, GREGORY	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/254,695.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S80

DETAILED ACTION

Claims 1-37 are pending and under consideration.

Information Disclosure Statement

An information disclosure statement (IDS) was received and entered on 12/11/03. The references listed have been considered.

Claim Objections

Claim 1 is objected to because it is ungrammatical. Articles should be inserted immediately before "polynucleotide" in line 13 and immediately before "target" in line 15.

Claim 6 is objected to because it is ungrammatical. An articles should be inserted immediately before "aqueous" in line 1 on page 78.

Claim 9 is objected to. Substitution of --or-- for "of" at line 20 is suggested.

Claim 10 is objected to because "sume" is misspelled.

Claims 13 and 17 objected to because "the said" is redundant.

Claim 16 is objected to because it is ungrammatical. Deletion of "by" is suggested.

Claim 17 is objected to because "foming" at line 18 and "inclduing" at line 24 are misspelled. Alos, "liposome" at line 22 should be plural.

Claim 26 is objected to. Substitution of --or-- for "of" at line 8 is suggested.

Claim 27 is objected to because "sume" is misspelled.

Claims 32 is objected to because "add' shold be --added--.

Claim 36 is objected to because "haemagglutin" is misspelled. Substitution of --haemagglutinin-- is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8, 17-32, and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8 are indefinite because claim 6 recites "the intravesicular space" without proper antecedent basis.

Claim 17 and dependents are indefinite because claim 17 recites "formed from liposome selected from the group consisting of lipids, cholesterol and non-ionic and cationic surface active agents". None of "lipids, cholesterol and non-ionic and cationic surface active agents" is a liposome. These are liposome-forming agents. The metes and bounds of the claim are also unknown because it is unlcear to what the phrase "present in an amount whereby the small unilamellar vesicles have an overall cationic charge" should be applied. This could be applicable only to "cationic surface agents" or it could be applicable to "cationically charged components". Claim 17 also recites "the intravesicular space thereof" without proper antecedent basis.

Claims 34 and dependents are indefinite because claim 34 recites "infection by target infections microbes". Did Applicant mean "target infectious microbes"? Claim 34 also recites "target microbe" without antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition to protect an animal against infection by hepatitis B or influenza, does not reasonably provide enablement for compositions to protect an animal against infection by human immunodeficiency virus (HIV) or hepatitis C virus (HCV). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 35 is drawn to a composition for administration to an animal to protect against infection by HIV or HCV. The composition comprises a nucleic acid encoding an antigen of HIV or HCV, and is expected to function as a vaccine against HIV or HCV.

Enablement of the claimed invention must be determined with respect to whether or not one of skill in the art could use the claimed compositions as intended, i.e. to protect against infection by HIV or HCV.

A review of the art shows that at the time of the invention, up to the present day, there was no protective vaccine against either HIV or HCV.

Barouch et al (Intervirology 2000 43: 282-287) who taught that, even though immune responses could be raised by DNA vaccination against HIV, these responses were not capable of protecting against HIV. See also Bende et al (AIDS Read. 10(9): 526-532 (9/2000), page 528, column 3, third full paragraph. Peters (Vaccine 20: 688-705, 2002) reviewed progress in making HIV immunotherapeutic vaccines, including DNA vaccines, and states that "[a]t present, there are no candidate vaccines that have been proven to significantly alter the natural history of an individual with HIV infection." See page 688, paragraph bridging columns 1 and 2. Peters also indicates that there is no evidence to suggest that any existing candidate vaccine is able to alter the rate of progression of HIV infection, and points out that observed effects on the immune system such as improved immune response against HIV, e.g. improved CTL response, are promising indicators but are not acceptable surrogate evidence of efficacy. This is an important consideration in interpreting studies on potential HIV therapeutic vaccines. In summary, it is clear that at the time of the invention, and afterwards, it was not routine in the art to obtain protection against HIV by administration of any vaccine including nucleic acid vaccines.

Abrignani (J. Hepatol. 31 (Suppl. 1): 259-263, 1999) stated that there was no vaccine for HCV. See first sentence of abstract. This finding is consistent with several other publications which indicate that despite a profound need for a HCV vaccine, none exists. The problems facing vaccine development include the fact that HCV has relatively low viremia (it is detectable only as RNA by PCR), HCV has high genomic diversity, and there is difficulty in assessing neutralizing antibody responses due to an

inability to grow HCV efficiently in culture. See Abrignani page 260, paragraph bridging columns 1 and 2, and column 2, first full paragraph; and Koff (Int. J. Parisitol. 33: 517-523, 2003) abstract. See also Prince (FEMS Microbiol. Rev. 14(3): 273-277, 1994) and Hunziker et al (Mol. Immunol. 38: 475-484, 2001).

The specification as filed provides no relevant guidance as to how to develop a vaccine against either HIV or HCV, suggesting only that such a vaccine should encode an antigen of either of the viruses such as HCV core protein. See page 6, lines 1-15. No guidance as to how to overcome the problems encountered in the prior art is provided. No working example is provided.

In view of the state of the art of HCV and HIV vaccine technology, development of a protective vaccine against either virus is considered to be highly unpredictable.

In view of the state of the art, the unpredictability in the art, and the lack of guidance or working examples, one of skill in the art could not use the claimed invention as intended without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6, 8-14, 16-21, 23, and 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618) in view of Kirby et al (Bio/Technology (1984), 2(11), 979-84).

Felgner taught methods of inducing an immune response in an animal by delivering compositions comprising cationic liposomes encapsulating polynucleotides that encode immunogens. See abstract; column 4 line 68 to column 5, line 24; paragraph bridging columns 6 and 7; column 7, lines 39, 40, and 49-56; paragraph bridging columns 7 and 8; particularly column 8, lines 3, 4, 7, and 21-31; paragraph bridging columns 17 and 18; and column 18, lines 30-53. The cationic liposomes comprise DOTAP, phosphatidylethanolamine, and dioleoylphosphatidyl-choline, and lipids of the general structures disclosed in claims 9, 10, 26, and 27. See for example paragraph bridging columns 13 and 14; and column 14, lines 37-46. Because Felgner taught that DNA encoding a polypeptide could be delivered to a cell for expression, Felgner is considered to fairly teach double stranded DNA since single stranded DNA is not expressed. Felgner taught delivery of mRNA at column 18, lines 12-18. Administration routes include intramuscular and subcutaneous. See column 20, lines 31-38 and column 22, lines 5-8.

Felgner did not teach liposomes having diameters in the range of 100-2000 nanometers, a dehydration rehydration method of liposomse synthesis.

Kirby taught a dehydration-rehydration method of encapsulating solutes such as DNA into liposomes. See abstract and Table 1 on page 980. Kirby also taught liposomes comprising a cationically charged component, a non-ionic component and a

zwitterionic ionic component, wherein the cationic component (stearylamine) was present at 10 mol% and conferred a positive charge on the liposomes. See Table 1 on page 980; and page 983, column 2, first sentence of second full paragraph. For DNA encapsulation, the DNA was mixed with empty, small unilamellar vesicles, the mixture was lyophilized, and subsequently rehydrated to form dehydration rehydration vesicles encapsulating DNA. See e.g. paragraph bridging columns 1 and 2 on page 983. Encapsulation efficiency of DNA was 72% +/- 8.5%. See Table 1. Vesicles made by this dehydration rehydration process averaged 0.30+/-0.28 microns in diameter, with a maximum size of 2 microns, and 95% of the particles being less than 1 micron. See page 982, column 2, lines 5-10. Kirby also taught a composition comprising 0.1-10 micrograms polynucleotide to mg of liposome-forming components (instant claim 14). See specification at page 15, lines 14-33, referencing Kirby at lines 14 and 28. This passage discloses incorporation in this range by mixing 16 micromoles of lipid with from 10-100 micrograms of DNA, and then performing the dehydration-rehydration procedure. Similarly, Kirby taught the formation of liposomes by addition of 8.25 micromoles of phospholipids with 50 micrograms of DNA. See Table 1 on page 980 which teaches that DNA was used at a concentration of 100 micrograms per ml, and that phospholipids were used at a concentration of 16.5 micromoles per ml; and page 983, column 2, lines 1-5 which disclose that lipids and material to be entrapped were combined in equal volumes of 0.5 ml each. Kirby also taught a separate step of separating unimcorporated materials from liposomes. See page 983, column 2, lines 16-22. In view of the 72% in corporation efficiency achieved by Kirby, about 18% of the

polynucleotide would be expected to be biob-entrapped and removed by the separation step.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the dehydration-rehydration method of Kirby to encapsulate DNA in liposomes for use in the method of Felgner. One would have been motivated to do so because the method of Kirby is a simple method which provides excellent encapsulation yields while using mild conditions. See title, page 979; column 1, lines 5-8 of second paragraph; and Table I on page 980. Also th emethod results in a greater proportion of oligo- and multilamellar vesicles which decrease the rate of loss of entrapped solutes (see paragraph bridging pages 982, and 983) and would be expected to exclude nucleases with greater success than unilamellar vesicles, thereby increasing the stability of the encapsulated nucleic acid.

Although the cited references are silent as to whether the stimulated immune response would involve both cell-mediated and humaoral responses, as required by claim 33, the cited art teaches all the required method steps, and the result is considered to be inherent in the steps.

Claims 3, 5, 15, 22, 24, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618 and Kirby et al (Bio/Technology (1984), 2(11), 979-84) as applied to claims 1, 2, 4, 6, 8-14, 16-21, 23, and 25-33 above, and further in view of Weiner (US Patent 5,593,972, filed 9/21/93).

The teachings of Felgner and Kirby are summarized above and can be combined to render obvious methods of inducing an immune response in an animal by administering intramuscularly or subcutaneously aqueous suspensions of cationic liposomes in the range of 100-2000 nm in diameter, wherein the liposomse encapsulate in their intravesicular spaces nucleic acids encoding an immunogen. The references also render obvious a means of making the liposomes by a dehydration-rehydration technique as in instant claims 6 and 8.

These references did not teach a plasmid comprising a promoter and encoding an immunogen, or an antigen of a microbe,

Weiner taught methods of causing an immune response in an individual by injection of a polynucleotide encoding an immunogen. In one embodiment the polynucleotide is a plasmid comprising a promoter and administered in a complex with a liposome. See column 1, lines 14-19; column 9, line 53 to column 10, line 8; column 10, lines 59-65; column 12, lines 6-13; and column 20, lines 37-39. Alternatively the polynucleotide is mRNA. See column 11, lines 23-28. The immunogenic polypeptide comprises an antigen of an infectious virus, such as HIV, influenza virus, hepatitis B virus and hepatitis C virus, or an antigen of a hyperproliferative cell associated with a hyperproliferative disease. See column 13, lines 5-13; column 14, lines 6-14; column 52, line 62 to column 56, line 21; and claims 1-7, columns 69 and 70. Weiner also discloses use of Hepatitis B virus surface antigen as an imunogen. See e.g. column 2, lines 55-60. The polynucleotide can be administered intramuscularly, or subcutaneously. See paragraphs bridging columns 16 and 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polynucleotides of Weiner in the invention of Felgner as modified by Kirby. One would have been motivated to do so because both Felgner and Weiner suggest that liposomal compositions should be used for *in vivo* delivery of nucleic acids encoding immunogens.

Claims 1, 2, 4, 6-14, 16-21, 23, and 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618 in view of Kirby et al (Bio/Technology (1984), 2(11), 979-84) and Collins (US Patent 5,567,433).

The teachings of Felgner and Kirby are summarized above and can be combined to render obvious methods of inducing an immune response in an animal by administering intramuscularly or subcutaneously aqueous suspensions of cationic liposomes in the range of 100-2000 nm in diameter, wherein the liposomse encapsulate in their intravesicular spaces nucleic acids encoding an immunogen. The references also render obvious a means of making the liposomes by a dehydration-rehydration technique as in instant claims 6 and 8.

Felgner and Kirby do not teach microfluidization of liposomes that is required in claim 7 and is embraced by claims 1, 2, 4, 6, 8-14 16-21, 23, and 25-33.

Collins taught a method of making dehydration-rehydration cationic liposomes for the purpose of encapsulating nucleic acids. See paragraph bridging columns 4 and 5, and column 5, lines 3-21. Microfluidization enhances the scale-up of liposome production. See column 6, lines 3-21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to microfluidize the liposomes as taught by Collins because microfluidization enhances the scale-up of liposome production, as noted above, thereby allowing production of greater amounts of vaccine.

Claims 3, 5, 15, 22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618, Kirby et al (Bio/Technology (1984), 2(11), 979-84), and Collins (US Patent 5,567,433) as applied to claims 1, 2, 4, 6-14, 16-21, 23, and 25-33 above, and further in view of Weiner (US Patent 5,593,972, filed 9/21/93).

The teachings of Felgner, Kirby, and Collins are summarized above and can be combined to render obvious methods of inducing an immune response in an animal by administering intramuscularly or subcutaneously aqueous suspensions of cationic liposomes in the range of 100-2000 nm in diameter, wherein the liposomse encapsulate in their intravesicular spaces nucleic acids encoding an immunogen. The references also render obvious a means of making the liposomes by a dehydration-rehydration technique including a microfluidization step as required by instant claim 7, and as is optional in instant claims 17 and dependents.

These references did not teach a plasmid comprising a promoter and encoding an immunogen, or an antigen of a microbe,

Weiner taught methods of causing an immune response in an individual by injection of a polynucleotide encoding an immunogen. In one embodiment the

polynucleotide is a plasmid comprising a promoter and administered in a complex with a liposome. See column 1, lines 14-19; column 9, line 53 to column 10, line 8; column 10, lines 59-65; column 12, lines 6-13; and column 20, lines 37-39. Alternatively the polynucleotide is mRNA. See column 11, lines 23-28. The immunogenic polypeptide comprises an antigen of an infectious virus, such as HIV, influenza virus, hepatitis B virus and hepatitis C virus, or an antigen of a hyperproliferative cell associated with a hyperproliferative disease. See column 13, lines 5-13; column 14, lines 6-14; column 52, line 62 to column 56, line 21; and claims 1-7, columns 69 and 70. Weiner also discloses use of Hepatitis B virus surface antigen as an imunogen. See e.g. column 2, lines 55-60. The polynucleotide can be administered intramuscularly, or subcutaneously. See paragraphs bridging columns 16 and 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polynucleotides of Weiner in the invention of Felgner as modified by Kirby and Collins. One would have been motivated to do so because both Felgner and Weiner suggest that liposomal compositions should be used for *in vivo* delivery of nucleic acids encoding immunogens.

polynucleotide is a plasmid comprising a promoter and administered in a complex with a liposome. See column 1, lines 14-19; column 9, line 53 to column 10, line 8; column 10, lines 59-65; column 12, lines 6-13; and column 20, lines 37-39. Alternatively the polynucleotide is mRNA. See column 11, lines 23-28. The immunogenic polypeptide comprises an antigen of an infectious virus, such as HIV, influenza virus, hepatitis B virus and hepatitis C virus, or an antigen of a hyperproliferative cell associated with a hyperproliferative disease. See column 13, lines 5-13; column 14, lines 6-14; column 52, line 62 to column 56, line 21; and claims 1-7, columns 69 and 70. Weiner also discloses use of Hepatitis B virus surface antigen as an imunogen. See e.g. column 2, lines 55-60. The polynucleotide can be administered intramuscularly, or subcutaneously. See paragraphs bridging columns 16 and 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polynucleotides of Weiner in the invention of Felgner as modified by Kirby and Collins. One would have been motivated to do so because both Felgner and Weiner suggest that liposomal compositions should be used for *in vivo* delivery of nucleic acids encoding immunogens.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.